Drug and Therapeutics Committee Training Course

Session 5: Drug Quality Assurance

Participant's Guide

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PURPOSE AND CONTENT

The purpose of quality assurance in public drug supply systems is to make certain that each drug reaching a patient is safe, effective, and of standard quality. Quality assurance activities in a hospital or clinic should be comprehensive, spanning the entire supply process from drug selection to patient use.

This session expands the participant's understanding of the determinants of drug quality. It emphasizes both the **technical** and **managerial** actions that can be employed to ensure drug quality and discusses the role of the Drug and Therapeutics Committee in ensuring quality of drugs in the health care system.

Objectives

After completion of this session, participants will be able to—

- Define drug quality
- Understand how drug quality is assessed
- Understand how drug quality is ensured
- Describe the role of the DTC in drug quality assurance

Preparation

Read:

- Participant's Guide
- *Managing Drug Supply*, Chapter 18, "Quality Assurance for Drug Procurement"
- *Managing Drug Supply*, Chapter 24, "Drug Management for Health Facilities"
- *Managing Drug Supply*, Chapter 26, "Transport Management"

Further Readings

- World Health Organization (WHO). *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Guidelines for Use*. WHO Drug Information 3:109–15. Geneva: 1989.

- WHO. *Basic Tests for Pharmaceutical Substances*. Geneva: 1991.

- WHO. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 31st Report. Technical Report Series, number 790. Geneva: 1990.

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- WHO. *Inland Stability Study (Sudan), Pilot Study 1989–1991*. Geneva: 1991.

- World Health Organization/United Nations Children's Fund (WHO/UNICEF). *Study on the Stability of Drugs During International Transport*. Geneva: 1991.

INTRODUCTION

The Drug and Therapeutics Committee is responsible for evaluation of new drugs before they are added to the formulary. As discussed in other sessions, this evaluation must involve efficacy, safety, quality, and cost. This session will provide information on how to evaluate and manage the quality of drugs being considered for the formulary.

The purpose of a quality assurance program for hospitals and clinics is to ensure that every drug reaching a patient is safe, effective, and meets quality standards. A comprehensive quality assurance program includes both technical and managerial activities from selection to patient use. Many areas within a health care system may be involved with quality assurance, including procurement, pharmacy, medical, and nursing departments, as well as the DTC.

Ensuring quality of a product is twofold:

1. *Obtaining* quality products that are safe and effective through structured selection and procurement methods

2. *Maintaining* quality products through the appropriate storage, distribution, monitoring, and prescribing methods

A comprehensive program will have the following important characteristics:

- Drugs are selected on the basis of safety and efficacy, in an appropriate dosage form with the longest possible shelf life.

- Suppliers with acceptable quality standards are selected.

- Drugs received from suppliers and donors are monitored to meet quality standards.

- Drug packaging meets contract quality specifications (blister packs, kits, bulk container specifications).

- Repackaging activities and dispensing practices maintain quality (appropriate containers and expiration dates).

- Adequate storage conditions in all drug areas are maintained.

- Transportation conditions are adequate (shipping conditions, temperature exposure).

- Product quality concerns reported by inventory managers, prescribers, dispensers, or patients are addressed and resolved.

Poor quality drugs may cause a number of serious problems including—

- Lack of therapeutic effect that may lead to prolonged illness or death.

- Toxic or adverse reactions may occur.

- Program credibility suffers extensively, making the entire health care system less effective and less desirable.

KEY DEFINITIONS

Drug Quality Assurance—Drug quality assurance may be defined as the sum of all activities and responsibilities required to ensure that the drug that reaches the patient is safe, effective, and acceptable to the patient.

Good Manufacturing Practice (GMP)—GMPs are performance standards that WHO and many national governments established for pharmaceutical manufacturers. GMPs are part of the quality assurance activities that ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and required by drug regulatory authorities. The standards include criteria for personnel, facilities, packaging, quality control, and, in most cases, stability testing.

Drug Quality Control—As defined by WHO, quality control is the part of the firm's process concerned with drug sampling, specifications, testing, and with the organization's release procedures that ensure that the necessary tests are carried out and that the materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

DETERMINANTS OR ASPECTS OF DRUG QUALITY

The following characteristics of a drug determine its quality:

- Identity—The correct active ingredient is present.

- Purity—The drug is not contaminated with potentially harmful substances.

- Potency—The correct amount of active ingredient is present, usually between 95 and 110 percent of the labeled amount.

- Uniformity—Consistency, color, shape, and size of the dosage form do not vary.

- Bioavailability—Bioavailability refers to the speed and completeness with which an administered drug enters the blood stream. This must be consistent to provide a predictable therapeutic result. Drug bioavailability differences exist between manufactures of the same product. Therefore, careful evaluation of generic drugs may be necessary before purchase and use.

- Stability—The activity of the drug is ensured for the period of time stated on the product label, that is, until the expiration date.

- Pharmacopoeial standard—A drug is of good quality if its characteristics meet the standards described in a widely accepted pharmacopoeia such as the British Pharmacopoeia (BP), European Pharmacopoeia, International Pharmacopoeia (IP), or United States Pharmacopeia (USP).

CRITICAL ELEMENTS OF A COMPREHENSIVE QUALITY ASSURANCE PROGRAM

How Is Quality Assessed?

Inspection of Shipments

All shipments of drugs should be quarantined and inspected thoroughly before released into the supply system. Inspection should include visual inspection and a review of product specifications (including expiration dates) to ensure that the drug meets specifications.

Laboratory Testing

Drugs should be tested in a laboratory to ensure they meet pharmacopoeial standards. Laboratory testing may not be necessary if reputable suppliers with high quality standards are utilized in the procurement of drugs. Pharmacopoeial standards can be found in international pharmacopoeias such as the British Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia, and the United States Pharmacopeia. Drugs that should be tested include—

- Therapeutically critical drugs (cardiovascular and emergency drugs)
- Drugs with known bioavailability or stability problems
- Drugs from new suppliers
- Drugs from suppliers that had quality problems in the past
- Random selection of other drugs to ensure quality

How Is Quality Assured?

Product Selection

Product selection should be guided by an effective DTC that has thoroughly evaluated the evidence-based information. Preferably only the dosage forms that have a long shelf life and are of acceptable stability and bioavailability should be selected.

Selection of Appropriate Suppliers

Suppliers need to be carefully selected and qualified so that reputable companies will be used to supply pharmaceuticals and medical supplies. In order to have the best suppliers, the following need to be done:

- Have the procurement department establish prequalification and registration of suppliers.
- For new suppliers, request samples of intended products before delivery for visual inspection and laboratory analysis.
- Request specific reports or data for certain drugs (e.g., bioavailability studies).
- Informally gather information from individuals and companies that have experience with the suppliers.

Product Certification

Obtain appropriate certification of all drugs before accepting for use, including—

- GMP certificate from drug regulatory authority, UNICEF Supply Division Warehouse Procurement and Assembly Center (UNIPAC), or other international agency
- Certificate of pharmaceutical product—WHO-type certificate from drug control agency of exporting country
- Batch certification—certificate of batch analysis or assay from manufacturer, drug regulatory agency, or other international quality control organization
- Random local testing—to confirm quality of the product received

Contract Specifications

Contract specifications for all drugs should include at a minimum—

- Pharmacopoeia reference standard
- Local language for product label if necessary
- Standards for packaging to meet specific storage and transport conditions

Appropriate Storage, Transport, Dispensing, and Use Procedures

Policies and procedures need to be in place to ensure the appropriate storage, dispensing, and use of all drugs. These procedures should include at a minimum an explanation of the following:

- Drug distribution and control procedures (inventory control and management)
- Provision for appropriate storage and transport
- Cold chain procedures that are enforced explicitly
- Appropriate dispensing and use procedures
  - Containers
  - Labeling
  - Counseling the patient
- Avoidance of repackaging unless appropriate quality control is in place

Product Monitoring System

The health care system needs a program to monitor the quality of drugs and medical supplies.

Product Problem Reporting System

All quality defects must be reported and the pharmacy or procurement department should keep files of these reports. Procurement, pharmacy, and the DTC should periodically evaluate these reports.

The Product Problem Reporting System should be established at the national or local level that specifies the following:

- Who should report the perceived product quality problem?
- How to fill in the reporting form.
- Where and to whom the reporting form should be sent.
- What additional measures need to be taken, such as sending samples or information concerning the quantities involved.
- What follow-up information will be provided to the person or facility that reported the problem.
- Under what criteria will a product receive further testing or be recalled?
- How to file and retrieve reports of product problems for future procurement needs?

Product Recalls

Product recalls will result from two sources: (1) internally, when a product reporting system identifies unacceptable quality of a product and (2) from the manufacturer or drug regulatory agency, indicating a product has been identified that no longer meets standards for efficacy, safety, or quality. The health care system needs a program to identify, retrieve, and return to the supplier any items that have been recalled or that do not meet quality specifications in the health care system.

A national and local program to handle product recalls, should include—

- Rapid communication to facilities for quick product recall
- Inventory control systems that track distribution to facilities by batch number
- Recalls classified according to risk to the consumer
  - Serious illness
  - Death
  - Temporary or mild illness
  - No adverse clinical effect
- Progress of a product recall to ensure complete compliance

Who Ensures Drug Quality?

Quality of products received in the health care system is the responsibility of many individuals and departments. The procurement department should take the lead role in this endeavor while the DTC must be an active advisor. The DTC should ensure that all of the departments and individuals listed below are working cohesively to ensure quality products are received.

Drug Regulatory Authority

- Registering drugs
- Inspecting manufacturers for GMP
- Inspecting pharmacies for compliance with national drug policies
- Sampling and testing drugs as needed

DTC

- Selecting drugs for the formulary and procurement
- Setting technical specifications for drug procurement
- Reviewing supply offers and assisting in selection of suppliers
- Reviewing storage and transportation facilities
- Coordinating drug quality testing
- Reviewing the quality defect reporting system

Hospital or Clinic Procurement Office

- Developing specifications for quality
- Prequalifying suppliers
- Inspecting products
- Reporting, tabulating, and taking action on quality defects

Pharmacy

- Controlling quality during repackaging
- Ensuring appropriate storage in the warehouse, pharmacy, and clinics
- Using appropriate containers for dispensing
- Instructing patients in appropriate use of drugs
- Reporting quality defects

Physicians

- Monitoring and promoting quality assurance in their facilities
- Reporting quality defects

Patients

- Storing drugs correctly
- Taking drugs correctly
- Reporting quality defects

IMPORTANT QUALITY ISSUES FOR THE DTC

Generic Substitution

An important function of the DTC is to obtain quality drugs at reasonable prices. The use of multiple-source generic products that are therapeutically equivalent to another product, but less expensive, is an important concept that will help control cost and maintain a high level of quality in drug selection. In this type of program, pharmacists are authorized to substitute products that have been prescribed by a physician with generic drugs that are considered therapeutically equivalent. It is important to note that a generic substitution program must provide substitutes that are equivalent in efficacy, safety, and quality.

A **therapeutically equivalent** product can be defined as a drug containing the same active ingredient in the same dosage form and of identical strength whose effects with respect to both safety and efficacy are essentially the same. Therapeutic equivalence implies that the product

has equivalent bioavailability or is bioequivalent. Generic drugs that have the same active ingredients may not have the same bioavailability.

Bioavailability refers to the speed and the extent of absorption of a drug's active ingredient in the blood stream. Bioavailability of generic products may differ between manufacturers of the same product. Drugs with known bioavailability problems are presented in Figure 1. It is important for procurement departments to obtain bioavailability data when ordering drugs and not to change manufacturers of a generic product unless bioequivalence of the new product can be assured. Bioavailability data, including laboratory test results, can be obtained from many manufacturers. Any requirements for this data should be included in the tender documents and final contracts with the suppliers.

The following are some examples of drugs known to have bioavailability problems among generic manufacturers.

Figure 1. Drugs with Known Bioavailability Problems

Aminophylline	Ergotamine	Levodopa	Quinidine
Ampicillin	Erythromycin	Levothyroxine	Rifampicin
Carbamazepine	Estrogens	Methyldopa	Spironolactone
Chloramphenicol	Furosemide	Nitrofurantoin	Theophylline
Chloroquine	Glibenclamide	Phenytoin	Warfarin
Digoxin	Iron sulfate	Prednisolone	
Dihydroergotamine	Isosorbide dinitrate	Prednisone	

Source: Adapted from Figure 18.1, *Managing Drug Supply*, 1997

See Session 9 for more discussion on generic and therapeutic substitution.

Stability of Drugs

Stability of a drug product is of considerable concern and refers to its capacity to maintain potency throughout the shelf life of the drug (until the expiration date). Stability can be ensured, to some degree, by asking for stability studies on products that have known problems and by ensuring that all products are received, stored, and transported at appropriate conditions, avoiding direct light, temperature extremes, and moisture. Reputable manufacturers will continue to test products throughout the stated shelf life to confirm that the drug retains its full potency.

Drugs with known stability problems must be handled carefully by the hospital or clinic. These drugs may deteriorate more rapidly than expected, especially in tropical conditions of elevated heat and humidity. Stability testing in the country of purchase may be necessary to ensure that these products indeed have stability throughout the shelf life of the product. Figure 2 presents a limited list of products that are known to have stability problems.

Figure 2. Drugs Found to Have Stability Problems under Tropical Conditions

Oral Solids (tablets)	Oral Liquids	Injectables
Acetylsalicylic acid (ASA)	Paracetamol	Ergometrine
Amoxicillin	Penicillin V suspension	Methylergometrine
Ampicillin		
Penicillin V tablets		
Retinol		

DRUG QUALITY ASSURANCE—IMPLICATIONS FOR THE DTC

The DTC is an important component of the hospital or primary care clinic quality assurance program. The DTC should have an active advisory role on all components of the quality assurance program to ensure that drugs are of the highest quality.

The following discussion focuses on those areas where the DTC should be the most involved and where it may have the most impact. These areas deal with defining product specifications, providing technical advice to the health care organization, and analyzing quality complaints.

Providing Technical Advice on Procurement of Pharmaceuticals

The DTC is responsible for evaluating and selecting drugs for the formulary and the hospital procurement list. Specific product specifications for procurement should be developed by the DTC and should include drug, strength, form, pharmacopoeial standard, bioavailability standard, and expiration dating. This information is best formulated by the DTC because this committee has the expertise and experience to provide the technical information that is required.

The DTC is also responsible for providing technical advice on supplier selection, storage of pharmaceuticals and biologicals, transportation methods to ensure quality, and laboratory testing of high-risk products.

Providing Technical Advice to Other Departments

The DTC should work closely with hospital and clinic departments, including phamacy, nursing, medical, and supply management staff, to ensure that drug quality assurance procedures are practiced throughout the system. All health care personnel should be enlisted and encouraged to participate in a comprehensive quality assurance program to ensure that drugs are procured, stored, administered, dispensed, and used correctly.

Analyzing Product Problem Reports

The DTC should work with drug regulatory agencies, the procurement department, suppliers, pharmacies, physicians, and patients to analyze, evaluate, and take action on quality complaints

of products. This function of the DTC is vital to ensure that drugs of good quality are available. Complaints about quality should be analyzed and recommendations developed to deal with quality defects. A drug recall system must be readily available and effective.

Even the best quality assurance program of a manufacturer, supplier, and a hospital or health clinic may have a defective product slip through the system. In addition to this, many health care professionals and patients will have erroneous perceptions of product quality (appropriate manufacturers, relationship of price and quality, etc), which makes the requirement for a monitoring system essential.

ACTIVITY

Activity 1: Quality Assurance Issues and Concerns

Participants should list the specific quality assurance concerns in their programs in hospitals and primary care clinics. List them under the following headings:

- Obtaining quality products (source issues): Problems with the quality of drugs being supplied by commercial sources, government production, or donors
- Maintaining quality products (supply system issues): Problems with quality assurance at the central warehouse, in transit, at local facilities, and the like
- Examples of poor quality: Anecdotes illustrating poor quality that do not clearly fit under the above headings

As a part of this exercise, please answer the following questions concerning your quality assurance programs:

1. Are you satisfied with the quality of drugs you receive?
2. Is quality maintained throughout your distribution network?
3. Are there complaints of poor quality by patients or health workers?
4. Is there a formal mechanism for reporting and investigating product quality complaints?
5. Does anyone have a particular quality assurance issue with which he or she needs help?
6. What role do you see for the DTC in improving and maintaining quality in your health care system?

SUMMARY

Quality assurance is the responsibility of many different programs and individuals, including procurement, pharmacy, medical staff, patients, and the DTC. It takes a coordinated effort to ensure that all departments work together in dealing with quality assurance. Drug quality assurance must have a high priority within the health care system in order for the hospital or clinic to have drugs that are effective, safe, acceptable in quality, and at reasonable cost. The consequences of poor quality products may lead to ineffective, inappropriate treatment or death as well as increased cost for the health care system. Increased cost is the result of the following:

- Additional laboratory testing
- Obtaining alternate suppliers and inventory to replace poor (or suspected poor) quality products
- Administrative time to deal with these products
- Direct cost of patients having to return to the health care system because a particular drug does not have a therapeutic effect

A comprehensive quality assurance program should be involved with *obtaining* quality products and *maintaining* this quality. The following activities are needed at a minimum to ensure that quality products are available to the patient.

Obtaining Quality	Maintaining Quality
Select drugs, dosage forms, and packaging to ensure quality.	Ensure proper storage conditions.
Use prequalified suppliers.	Hasten port clearing.
Prepare and enforce quality-related contract specifications.	Ensure proper transportation conditions.
Request product samples before purchasing.	Counsel patient on appropriate use, storage.
Inspect shipments before acceptance.	Use proper dispensing containers with clearly written labels.
Perform laboratory tests on vital drugs.	Involve health workers in quality assurance, including appropriate storage, transportation, and use.
	Use formal reporting system for product quality defects.
	Follow up and test suspect products.